REMARKS

Claims 24-27, 29 and 32-36 were pending in the application.

Claims 25 and 32-36 were cancelled without prejudice to presentation in related applications.

Claims 24 and 27 were amended to further clarify the claimed invention. Claim 24 was also amended to recite a functional feature of the claimed sequences, support for which can be found throughout the application as filed including, for example, in paragraphs [0032], [0037], [0091] and [0195]. Applicants further note that at the time of filing it was well-known that Egr1 (early growth response gene 1) is a transcription factor (see, for example, the Eid *et al* reference).

No new matter has been added.

Upon entry of this amendment, claims 24, 26, 27 and 29 will be pending.

Withdrawn Rejections

Applicants note with appreciation the withdrawal of the rejections of claims 24-27 and 29 under 35 U.S.C. §112, second paragraph, for the recitation of the phrases "of an unaffected individual", "the level of mRNA in (a)", "a level of the mRNA in a second sample", and "a level of the mRNA in a third sample", and of claims 24-27 and 29 under 35 U.S.C. §102(b)

Rejections under 35 U.S.C. §112, second paragraph

Claims 24-31 remain rejected under 35 U.S.C.§112, second paragraph. The Office alleges that with respect to the recitation in the rejected claims of the phrase "... a decrease of at least 50% [100% in claim 29] between the level of the nucleotide sequence in (a) and the level of the nucleotide sequence in the sample indicates that the patient has colon cancer" that it is "unclear whether colon cancer tissue exhibits decreased expression of SEQ ID NO:167 nucleotide as compared to normal colon tissue or whether normal colon tissue exhibits decreased expression of SEQ ID NO:167 nucleotide as compared to colon cancer tissue expression constitutes a 50% decrease." Applicants do not agree.

As set forth in Applicants' previous response, one of skill in the art would readily understand that colon cancer is indicated in tissue exhibiting decreased expression of SEQ ID NO:167 nucleotide less by at least 50% than expression of SEQ ID NO:167 nucleotide in normal colon tissue. However, in an attempt to advance the prosecution of the pending claims to allowance, Applicants have amended claims 24, 27 and 29 to further clarify that decreased expression of SEQ ID NO:167 nucleotide in a patient sample (as compared to the level of expression of SEQ ID NO:167 nucleotide in normal colon tissue) is indicative of colon cancer.

Applicants invite the Examiner to contact the undersigned if the claim language is deemed to be amenable to further clarification.

In view of the foregoing, Applicants respectfully request the withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §112, first paragraph (enablement)

Claims 24-27 and 29 and new claims 32-36 were rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the enablement requirement. The Office acknowledges that the claims are enabled:

> for a method of diagnosing prostate cancer comprising determining the level of a nucleotide sequence comprising SEQ ID NO:167 in a patient sample ... and comparing said level to the level of nucleotide sequence comprising SEQ ID NO:167 in non-cancerous prostate tissue, wherein a decreased level of nucleotide sequence comprising SEQ ID NO:167 in the non-cancerous prostate tissue as compared to the patient sample indicates that the patient has prostate cancer ...".

However, the Office alleges that the specification is not enabled for methods of diagnosing colon cancer, methods for diagnosing prostate cancer (by comparing patient samples to "non-cancerous colon tissue samples"), or methods for diagnosing prostate cancer (by comparing patient samples to "non-cancerous prostate samples"). (Office Action, page 7, underlining in original). Applicants do not agree.

Preliminarily, Applicants note that claims 25 and 32-36 were cancelled without prejudice, rendering the rejections moot to the extent they refer to such claims. Claims 24 and 27 were amended to recite that decreased expression in the patient colon tissue sample as compared to the control colon sample is indicative of colon cancer.

The Office alleges that undue experimentation would be required for a person skilled in the art to practice the claimed invention. The Office notes that "if a molecule ... is to be used as a surrogate for a diseased state, some disease state must be identified in some way with the molecule." The Office also alleges that the Eid et al. reference:

> *clearly* teaches an example that demonstrates elevated levels of nucleotide sequences comprising SEQ ID NO:167 are found in prostate tissue samples from patients with prostate cancer as compared to levels of said sequences in non-cancerous prostate tissue samples. ... [and] that [t]he art does not hint or suggest that a decrease in expression of nucleotide sequences comprising SEQ ID NO:167 in prostate tissue samples, as compared to any type of control, would predictably indicate that the patient has prostate cancer"

(Office Action, page 16; emphasis in original). Applicants do not agree as no undue experimentation would be required for a person of skill in the art to practice the presently claimed methods.

To practice the invention, the skilled artisan need only determine if the level of nucleotide sequences comprising SEQ ID NO:167 in colon tissue samples from patients samples is at least 50% lower than the level of said sequences in non-cancerous colon tissue samples. Patient samples with such lowered levels compared to non-cancerous colon samples are indicative of colon cancer

With respect to the Office's requirement that a disease state be identified in some way with the molecule, Applicants respectfully point out that this correlation has been provided. First, Applicants note that the application as filed correlates Egr1 misexpression with cancer. Other references support the correlation of down-regulation of Egr1 with colon cancer and provide the disease state-molecule link requested by the Office.

For example, Tice et al. (J. Biol. Chem., 2002, February 22, 277. 8:6118-6123) notes that Egr-1 expression is decreased in 9 out of 12 tumor samples from patients with colon cancer as compared to a non-cancerous control. A study published in 2005 by Jens Karsten Haberman confirms that gene expression levels of EGR1 are significantly reduced in colorectal cancer as compared to control (see, for example, page 57). Copies of the references cited above are included in a supplemental IDS filed concurrently with this response.

Measurement and comparison of levels of nucleotide sequences comprising SEQ ID NO:167, or full complements, thereof would not require undue experimentation, given the knowledge of one of skill. Accordingly, one skilled in the art would understand that any experimentation, if required, would be very amenable to automation. Applicants also remind the Office that in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the court discussed the adequacy of disclosure with regard to a patent disclosing an immunoassay method for the detection of hepatitis B antigen using monoclonal antibodies. The *Wands* Court noted that of 143 hybridomas produced, only nine were assayed and, of those, only four hybridomas secreted IgM antibodies and exhibited a binding affinity constant for the HBsAg determinants of at least 10^9 M^{-1}, a "respectable 44 percent rate of success." *In re Wands*, 8 USPQ2d at 1406. Finding the claims were enabled, the Wands Court stated:

> Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.
>
> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen.

In re Wands, 8 USPQ2d at 1406 (emphasis added). Therefore, where the art typically engages in a complex, but routine degree of experimentation, having to do so is not the undue

experimentation proscribed by 35 U.S.C. § 112, first paragraph, under the reasoning of *In re Wands*. Even assuming, *arguendo*, that performing experiments to confirm the correlation reported by Applicants between increased expression of SEQ ID NO: 167 and colon cancer is considered "complex" (Applicants respectfully assert that the experimentation is not "complex"), Applicants submit that this kind of experimentation, although complex, is routine in the art, and therefore, is not undue experimentation.

In view of the foregoing, Applicants respectfully requests withdrawal of the enablement rejection.

Claim Objections

Claims 29 and 36 were objected to for allegedly failing to further limit the subject matter of the claims on which they depend. Claim 36 was cancelled without prejudice, rendering the objection moot to the extent it applies to claim 36.

Claim 29 further limits that subject matter of claims 24 and 27. Claims 24 and 27 recite methods for determining whether a patient has colon cancer: decreased expression (by at least 50%) of nucleotide sequences comprising SEQ ID NO:167 in the patient tissue sample as compared to the patient control sample is indicative of colon cancer. Claim 29 is narrower in scope than either of claims 24 or 27, specifying that colon cancer is indicated when decreased expression (by at least 100%) of nucleotide sequences comprising SEQ ID NO:167 in the patient tissue sample as compared to the patient control sample is indicative of colon cancer. Because a method that would infringe claims 24 or 27 would not necessarily infringe claim 29 (for example, decreased expression of nucleotide sequences comprising SEQ ID NO:167 of 77% in the patient sample as compared to the control colon sample), claim 29 does further limit the subject matter of the claims from which it depends.

Accordingly, Applicants respectfully request the withdrawal of the objection to the claims.

Rejections under 35 U.S.C. §112, first paragraph (written description)

Claims 24, 25, 27, 29, 32, 33, 35 and 36 were rejected as allegedly failing to comply with the written description requirement. The Office alleges that although the application provides written description for sequences comprising SEQ ID NO:167 and the full complement thereof, written description is allegedly lacking for sequences at least 98% or at least 99% identical to SEQ ID NO:167 and a complement thereof. Applicants respectfully traverse.

Preliminarily, as set forth above, claims 25 and 32-36 were cancelled without prejudice. Claims 24 and 27 were revised to further clarify in which sample a decrease in expression levels is observed, to recite that the "complement" is a "full complement", and to recite a functional characteristic of the claimed sequences.

With respect to the Office's comments regarding 98% homologs, Applicants respectfully assert that adequate written description is provided in the application as filed. As discussed above, claim 24 was amended to specify that the 98% homolog has the same cell proliferation activity as SEQ ID NO:167. Thus, the pending claims recite structural and functional features common to the members of the claimed genus. A person skilled in the relevant art would understand that Applicants had possession of the claimed polynucleotides.

In view of the foregoing, Applicant respectfully requests withdrawal of the written description rejection.

New Matter

Claims 25 and 33 were rejected under 35 U.S.C §112, first paragraph as allegedly containing new matter. Claims 25 and 33 were cancelled without prejudice, thereby rendering the rejection moot.

Rejections Under 35 U.S.C. §102

Claims 35 and 36 stand rejected as allegedly anticipated by Eid et al. (Cancer Research 58, 2461-2468) as evidenced by Monia et al. (U.S. Patent 6,008,048). Applicants do not agree.

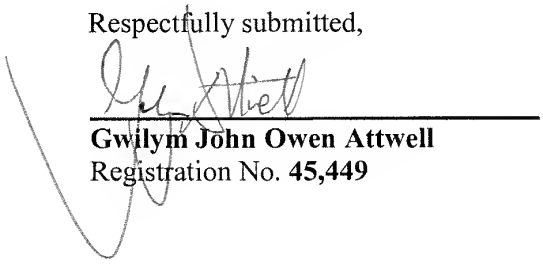
Notwithstanding, claims 35 and 36 were cancelled without prejudice, thereby rendering the rejection moot.

Conclusion

The foregoing represents a bona fide attempt to advance the present application to allowance. Applicants respectfully assert that all claims are in condition for allowance, which action is hereby requested. The Examiner is invited to telephone the undersigned attorney at (302) 778-8458 if such would expedite prosecution.

Please apply any charges or credits to Deposit Account 06-1050.

Respectfully submitted,



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